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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,236	12/02/2003	Jennifer Lockridge	MBHB01-1735-B (400.140)	4026

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
06/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/726,236	LOCKRIDGE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on June 11, 2007 has been entered.

Claims 1-8 and 10-26 are pending in the instant application.

Claims 1-8 and 10-26 have been examined on the merits.

Response to Arguments

Applicant's Amendment and Response mailed June 11, 2007 have been considered. Rejections and/or objections not reiterated from the previous Office Action mailed December 11, 2006 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Priority

It is noted that in Applicant's request for continued examination under 37 CFR 1.114 filed June 11, 2007, Applicants have provided extensive remarks regarding SEQ ID NO:14 of the instant invention. Specifically, at page 5 of Applicant's Remarks filed

June 11, 2007, Applicants disclose that "SEQ ID NO:14 represents GenBank NM_002019". Applicants go on to provide a copy of a review of the GenBank database regarding GenBank Accession No. NM_002019, said Accession No. being 7,860 basepairs in length (see Applicant's Remarks filed June 11, 2007 at page 4). In fact, Applicants disclose, "GenBank Accession No. NM_002019 is identified as an "mRNA" sequence having 7,680 nucleotides" (see Applicant's Remarks filed June 11, 2007 at page 4, last paragraph). The Examiner would like to point out that the sequence of GenBank Accession No. NM_002019 was submitted and made of record on the information disclosure statement filed December 2, 2003, said Accession No. being 7,680 nucleotides in length.

Now then, referring to SEQ ID NO:14 of the instant invention, it is noted that the sequence is only 5,777 basepairs in length. Given Applicant's disclosures regarding SEQ ID NO:14, as it relates to GenBank Accession No. NM_002019, and the fact that the Accession No. was made of record as being 7,680 basepairs, it does not appear that the two sequences are the same since one sequence is 7,680 nucleotides in length and the other sequence is only 5,777 nucleotides in length.

Next then, referring to a recent review of the GenBank database regarding GenBank Accession No. NM_002019, the following information is disclosed:

NCBI Sequence Viewer v2.0

```
LOCUS       NM_002019                5777 bp    mRNA    linear   PRI 03-JUN-2007
DEFINITION  Homo sapiens fms-related tyrosine kinase 1 (vascular endothelial
            growth factor/vascular permeability factor receptor) (FLT1), mRNA.
ACCESSION   NM_002019
VERSION     NM_002019.2  GI:32306519
KEYWORDS    .
SOURCE      Homo sapiens (human)
```

In summary, Applicants contend that SEQ ID NO:14 represents GenBank NM_002019, as detailed throughout Applicant's Remarks filed June 11, 2007. It is noted that SEQ ID NO:14 is a different sequence from GenBank Accession No. NM_002019 since the former appears to be a substantially shorter sequence than the latter. Furthermore, a recent review of the GenBank database regarding GenBank Accession No. NM_002019 reveals that this sequence is 5,777 nucleotides in length, not 7,680 nucleotides in length as Applicants contend. In this regard, none of the parent applications that Applicants claim priority to have support for GenBank Accession No. NM_002019 since it cannot be determined what sequence the Accession No. actually consists of. Therefore, the instant application and claims have been given priority to the filing date of the instant application, which is December 2, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 10-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims are drawn to a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14. It is noted that SEQ ID NO:14 was added to the sequence listing in the Amendment filed on September 20, 2006. The Examiner would like to point out that Applicants disclose, "SEQ ID NO:14 represents GenBank NM_002019" (see Applicant's Remarks filed June 11, 2007 at page 5). Applicants go on to provide a copy of a review of the GenBank database regarding GenBank Accession No. NM_002019, said Accession No. being 7,860 basepairs in length (see Applicant's Remarks filed June 11, 2007 at page 4). In fact, Applicants disclose, "GenBank Accession No. NM_002019 is identified as an "mRNA" sequence having 7,680 nucleotides" (see Applicant's Remarks filed June 11, 2007 at page 4, last paragraph). The Examiner would like to point out that the sequence of GenBank Accession No. NM_002019 was submitted and made of record on the information disclosure statement filed December 2, 2003, said Accession No. being 7,680 nucleotides in length.

Now then, referring to SEQ ID NO:14 of the instant invention, it is noted that the sequence is only 5,777 basepairs in length. Given Applicant's disclosures regarding SEQ ID NO:14, as it relates to GenBank Accession No. NM_002019, and the fact that the Accession No. was made of record as being 7,680 basepairs, it does not appear that the two sequences are the same since one sequence is 7,680 nucleotides in length and the other sequence is only 5,777 nucleotides in length.

Next then, referring to a recent review of the GenBank database regarding

GenBank Accession No. NM_002019, the following information is disclosed:

NCBI Sequence Viewer v2.0

```
LOCUS       NM_002019                5777 bp    mRNA    linear   PRI 03-JUN-2007
DEFINITION  Homo sapiens fms-related tyrosine kinase 1 (vascular endothelial
            growth factor/vascular permeability factor receptor) (FLT1), mRNA.
ACCESSION   NM_002019
VERSION     NM_002019.2  GI:32306519
KEYWORDS    .
SOURCE      Homo sapiens (human)
```

In summary, Applicants contend that SEQ ID NO:14 represents GenBank NM_002019, as detailed throughout Applicant's Remarks filed June 11, 2007. It is noted that SEQ ID NO:14 is a different sequence from GenBank Accession No. NM_002019 since the former appears to be a substantially shorter sequence than the latter. Furthermore, a recent review of the GenBank database regarding GenBank Accession No. NM_002019 reveals that this sequence is 5,777 nucleotides in length, not 7,680 nucleotides in length as Applicants contend. In this regard, SEQ ID NO:14 appears to be new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 10-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavco et al. (Clinical Cancer Research, 2000 Vol. 6:2094-2103), in view of Scherer et al. (Nature Biotechnology, 2004 Vol. 21:1457-1465), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001), Matulic-Adamic et al. (U.S. Patent No. 5,998,203), and Reich et al. (Current Opinion in Genetics and Development, 2003 Vol. 13:317-322).

Claim 1 is drawn to a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14. Claims 2-8 and 10-26 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein said tissue is ocular tissue; wherein said cell is an ocular cell; wherein said ocular tissue is retinal tissue; wherein said ocular cell is a retinal cell; wherein said double stranded RNA is administered to said tissue or cell via injection; wherein said injection comprises intraocular injection; wherein said VEGFR is VEGFR1; wherein said double stranded RNA is chemically

synthesized; wherein said double stranded RNA comprises at least one nucleic acid sugar modification; wherein said sugar modification comprises a 2'-deoxy-2'fluoro modification, a 2'-deoxy modification, a 2'-O-alkyl modification, a 2'-O-methyl, or a 2'-O-allyl modification; wherein said double stranded RNA comprises at least one nucleic acid base modification or at least one nucleic acid backbone modification; wherein said backbone modification comprises a phosphorothioate internucleotide linkage; wherein said double stranded RNA comprises at least one non-nucleotide; wherein said non-nucleotide comprises an abasic moiety; wherein said abasic moiety is present at the 3'-end, 5'-end or both the 3'- and 5'- ends; wherein said double stranded RNA comprises a cap structure at the 3'-end, 5'-end or both the 3'- and 5'- ends; wherein said cap is an inverted nucleotide, an inverted abasic moiety, or an inverted deoxyabasic moiety.

Applicant is reminded that the instant claims have been afforded priority to the filing date of the instant application, which is December 2, 2003. Also, the Examiner would like to point out that the instant specification at page 21, last paragraph discloses, "The term "double stranded RNA" or "dsRNA" as used herein refers to a double stranded RNA molecule capable of RNA interference "RNAi", including short interfering RNA "siRNA"". Therefore, given this disclosure, the Examiner is interpreting the term "double stranded RNA" to only include and encompass a double stranded RNA molecule capable of RNA interference.

Pavco et al. teach a method of locally administering to a tissue or cell a chemically synthesized double stranded hammerhead ribozyme comprising a nucleotide sequence that is complementary to a nucleotide sequence encoding a VEGFR1

encoding RNA (see page 2095, second column and page 2096). It is noted that the ribozyme was administered i.v. by continuous infusion. It is further noted that the VEGFR1 ribozyme is targeted to SEQ ID NO:14 of the instant invention (see Table 1 where Accession Number X51602 is identical to the 7,680 nucleotide sequence of GenBank Accession No. NM_002019).

Pavco et al. do not teach a double stranded RNA molecules capable of RNA interference, a double stranded RNA molecule capable of RNA interference that comprise chemical modifications, or delivery of a double stranded RNA molecule capable of RNA interference to ocular cells or tissues.

Scherer et al. teach the use of nucleic acid-based inhibitors, including double stranded ribozymes and double stranded RNA molecules capable of RNA interference, as antisense agents for sequence-specific mRNA knockdown. Scherer et al. also teach that double stranded RNA molecules capable of RNA interference are more potent than double stranded ribozymes for targeted message destruction (see page 1461, first column).

Elbashir et al. teach double stranded RNA molecules capable of RNA interference which comprise 2'-deoxy modifications or 2'-O-methyl modifications (see Figure 4).

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures (see Abstract). The double stranded nucleic acid RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a

target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the double stranded nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3'-phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'-deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Reich et al. teach a review of gene therapy for ocular neovascularization for the treatment of age-related macular degeneration and diabetic retinopathy. Specifically, Reich et al. teach injection techniques used to deliver gene therapy agents, including antisense agents, to retinal tissues and cells (see Figure 1 and page 319).

It would have bee *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to devise a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14 using the teachings of Pavco et al. and Reich et al. and following the motivations of Scherer et al. and Elbashir et al.

One of ordinary skill in the art would have been motivated to devise a method of locally administering to a cell or tissue a double-stranded RNA complementary to a

nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14 since Pavco et al. taught that such a method reduces the growth and metastatis of solid tumors *in vivo*. One of ordinary skill in the art would have been motivated to substitute the double-stranded hammerhead ribozyme taught by Pavco et al. with the double stranded RNA molecule capable of RNA interference of the instant invention since Scherer et al. taught that double stranded RNA molecules capable of RNA interference are more potent for targeted message destruction than ribozymes. Further, one of ordinary skill in the art would have been motivated to substitute the double-stranded hammerhead ribozyme taught by Pavco et al. with the double stranded RNA molecule capable of RNA interference of the instant invention since it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

One of ordinary skill in the art would have been motivated to modify the double stranded RNA molecule to include, for example, 2'-deoxy modifications, 2'-O-methyl, 2'-O-allyl modifications, phosphorothioate internucleotide linkages, or abasic moieties since such modifications were known in the art to add benefits to double stranded nucleic acids such as protection from exonuclease degradation and improve uptake of the nucleic acid, as taught by Elbashir et al. and Matulic-Adamic et al. The cited art demonstrates that the specific modifications were extensively described in the art. One of skill in the art would be motivated to test modifications that are known to benefit oligonucleotide stability and delivery and apply each of them to a double stranded nucleic acid molecule in order to optimize the overall stability and delivery route of the

nucleic acid. One of ordinary skill in the art would have been motivated to deliver the double stranded RNA molecule to ocular cells or tissues since Reich et al. taught that such delivery methods could result in treatment of macular degeneration and retinopathy in humans.

One of ordinary skill in the art would have expected success at devising a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14 since, at the time the invention was made, Pavco et al. taught the successful use and design of a method of locally administering to a cell or tissue a nucleic acid-based inhibitor complementary to a nucleotide sequence of a VEGF receptor comprising SEQ ID NO:14. One of ordinary skill in the art would have expected success at using a double stranded RNA capable of RNA interference in the method taught by Pavco et al. since Scherer et al. taught the successful use of nucleic acid-based inhibitors, including double stranded RNAs capable of interference in the knockdown of gene expression and Elbashir et al. taught the successful use and design of double stranded RNAs capable of interference for mediating RNAi. There would be a reasonable expectation of success to apply each of the claimed modifications to the double stranded RNA capable of interference because the chemistry was well known to one of ordinary skill in the art at the time the invention was made (see Elbashir et al. and Matulic-Adamic et al.) and merely selecting combinations of such modifications is considered a design choice. One of ordinary skill in the art would have expected successful at administering the double stranded RNAs capable of interference to ocular cells and tissues since Reich et

al. taught how to successfully use antisense gene therapy agents for treatment of complications of neovascularization of the iris in human patients.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

tcg
June 15, 2007

/Terra Cotta Gibbs/